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To the Editor,

Repeated clinical trials on a single medical intervention are never exact replications because patients differ and there are usually some variations in the intervention and outcome measurements. Such variations can lead to inconsistent results between studies on the same intervention.

Drs Serghiou and Goodman [1] proposed random-effects meta-analysis as a solution to summarize inconsistent results. However, a long-term concern in meta-analysis has been the apples-and-oranges comparison problem when studies that are too different are combined into a single estimate of effect. Random-effects meta-analysis can exacerbate this problem.

Serghiou and Goodman mentioned that many statisticians have encouraged the use of subgroup analysis to search for explanations for heterogeneity, but they devalued such an approach by stating that subgroup analyses are exploratory and their results should be interpreted accordingly.

Few meta-analyses lead to direct changes in clinical practice, but many meta-analyses can guide further research. If all inconsistent studies are combined into a single confidence interval, there is no guidance for new trials. In contrast, when a subgroup analysis finds differences in the treatment effect by certain characteristics of the trials, such findings can guide further research. I will illustrate these differences in the following examples.

One meta-analysis on vitamin C and postoperative atrial fibrillation used the random-effects meta-analysis approach to describe data from 13 trials and calculated that vitamin C was associated with a decreased occurrence of postoperative atrial fibrillation with a relative risk (RR) of 0.68 (95% CI 0.54–0.87). However, heterogeneity was significant with an I^2 of 59% (P = 0.003).[2] Although the confidence interval indicates that vitamin C was associated with a decreased risk, at least in some hospital contexts, it is not evident which patients should take vitamin C or which patient groups should be investigated in further trials.

Another meta-analysis used the subgroup analysis approach and calculated that among 5 trials conducted in the United States, vitamin C did not prevent postoperative atrial fibrillation (RR 1.04; 95% CI 0.86–1.27). However, in 9 trials conducted outside the United States in lower-income countries, vitamin C was associated with a decreased incidence of postoperative atrial fibrillation (RR 0.56; 95% CI 0.47–0.67).[3] These subgroup findings indicate that new trials in the United States may be a waste of resources, whereas further research conducted in lower-income countries should be encouraged. Such conclusions cannot, however, be drawn from the single confidence interval from the random-effects meta-analysis.

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